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Streptococcal hypersensitivity reloaded: severe inflammatory syndrome in Behçet's disease following 23-valent polysaccharide *Streptococcus pneumoniae* vaccine

SIR, Infections with *Streptococcus pneumoniae* are a significant cause of morbidity and mortality in patients with autoimmune inflammatory rheumatic diseases. The European League Against Rheumatism (EULAR) recommends the 23-valent polysaccharide pneumococcal vaccine (23-PPV) in patients with inflammatory rheumatic diseases, including Behçet's disease (BD) [1]. Pneumococcal vaccine safety was tested in RA, juvenile arthritis and SLE [2] and no significant local or systemic adverse events and disease flares were reported.

We have recently implemented the EULAR recommendations in our outpatient service by systematically vaccinating patients with autoimmune inflammatory rheumatic diseases if they are treated with immunosuppressive agents. Subsequently we have observed four patients with BD who developed severe local reactions to the first application of 23-PPV at the injection site as well as a severe systemic inflammatory response. No systemic adverse reactions were observed in patients of our service who received 23-PPV for autoimmune conditions other than BD.

The clinical features of the four patients are summarized in Table 1. The three male patients fulfilled the criteria for BD and the female patient had an incomplete phenotype of BD with oral ulcers, oligoarthritis and HLA-B51 genotype positivity. The mean disease duration of BD was 9.5 years. All of the patients had been vaccinated against influenza and tetanus without complication, one also had received hepatitis A and tick-borne encephalitis vaccines without adverse reactions. The local adverse reaction to the 23-PPV originating from different charges was similar in all of the patients and developed ~4–8 h after the injection, with pain, redness and local swelling (spreading ~15 cm from the injection site); urticarial lesions were not observed. Whereas the local symptoms resolved completely after ~1 day in the female patient, the three males developed a severe systemic inflammation with malaise, high fever, chills and vomiting. Leucocyte counts increased to a maximum of $20.5 \times 10^9/l$ and the CRP to

385 mg/l. All symptoms resolved in a few days with local cooling, paracetamol, anti-inflammatory non-steroidal drugs and i.v. fluids. In one patient, the initially diffuse swelling at the injection site, which extended from the acromion to the elbow, turned into a profound pseudofolliculitis, prior to complete resolution (supplementary figure).

There are several possible explanations for this severe adverse reaction. Pneumovax 23 is the currently licensed pneumococcal polysaccharide vaccine. A 0.5 ml dose of this vaccine contains 25 µg of polysaccharides from the 23 most prevalent or invasive pneumococcal types in isotonic saline, plus 0.25% phenol as preservative. Minor local injection reactions are frequently observed, whereas the incidence of severe vaccine-related systemic adverse events is low. Phenol is used in many vaccines as a preservative with low immunogenic properties. It is therefore unlikely that phenol contributed to the adverse reactions.

BD is considered an autoinflammatory multisystem disease. An overreacting immune system with neutrophil hyperfunction, also described as pathergy, is frequently encountered. For pathergy testing, a sterile needle is used to obliquely penetrate the skin, provoking a local induration after 48 h. Pathergy-like inflammatory reactions can also be triggered by insults such as trauma, arthrocentesis or surgery, and then affect organs other than the skin [3]. However, three of the reported patients here had negative pathergy testing.

In patients with BD, elevated antibody titres directed against streptococci in the oral flora have been detected and skin hypersensitivity against streptococci has been included in the Japanese diagnostic criteria for BD [4]. An immune reaction to one or several of the 23 polysaccharides by pre-existing anti-streptococcal antibodies or an IgE-mediated anaphylactic reaction could therefore explain some symptoms of the patients, although the time course and the clinical features make the latter pathomechanism unlikely. The systemic inflammatory reactions in our cohort contrast to reports of local BD symptoms that occurred after streptococcal antigen exposure [5]. This divergence may be accounted by the obvious difference in the streptococcus species, as well as by different amounts of antigen and route of exposure. Interestingly, the mildest reaction was observed in the patient with incomplete BD who only received ibuprofen. To what extent etanercept, abatacept or AZA further influenced the symptoms in the other three patients remains speculative at this point.

More recently, BD has been proposed as an autoinflammatory disease secondary to an aberrant activation of the inflammasome, a complex modular structure that activates IL-1β [6]. In this context, it is interesting to note that 23-PPV can activate toll-like receptors (TLRs) 2 and 4 as known triggers of sterile inflammation [7]. TLR triggering by 23-PPV components with subsequent inflammasome activation via IL-1β in a predisposed host could explain the rapid onset of the adverse reaction, the occurrence of high fever and the neutrophilic nature of the systemic inflammatory response. Our observations may also

TABLE 1 Clinical characteristics of four patients with features of BD who developed severe inflammation after receiving 23-valent pneumococcal vaccination

Age, years/ gender	Origin	Clinical presentation of BD	Disease duration, years	HLA allele	Pathergy testing	BD treatment at vaccination	Symptoms after vaccination
32/male	Swiss	Recurrent aphthous oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgia, thrombophlebitis, cerebral venous thrombosis, retinochoroiditis	11	B51+	ND	Abatacept, prednisolone (20 mg)	Day 1: ipsilateral axillar pain, redness, calor and tenderness at the injection site Day 2: fever (40.0°C), chills, nausea and vomiting, CRP 385 mg/l Day 3: pseudofolliculitis at injection site (supplementary figure)
41/male	Turkish	Recurrent aphthous oral ulcers, genital ulcers, arthritis, erythema nodosum, pseudofolliculitis	6	ND	Negative	Etanercept	Day 1: local pain, calor, redness and swelling, fever (38.9°C), CRP 223 mg/l, headache, shivering, dyspnoea
41/female	Turkish	Recurrent aphthous oral ulcers, oligoarthritis	6	B51+	Negative	Ibuprofen	Day 1: local pain, calor and swelling at injection site after 1 h
46/male	Turkish	Recurrent aphthous oral ulcers, pseudofolliculitis, thrombophlebitis, uveitis	15	B51+	Negative	AZA	Day 1: local pain, calor, swelling, fever (40°C), asthenia, CRP 158 mg/l

ND: no data.

have implications for other autoinflammatory diseases [6]. We suggest that the safety of pneumococcal vaccination with 23-PPV in BD patients should be further investigated.

Rheumatology key message

- Pneumococcal vaccine can trigger severe inflammation in BD, possibly by inflammasome activation.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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EF/SSc overlap syndrome and aplastic anaemia resistant to immunosuppressive therapy

SIR, EF (Shulman syndrome) is a rare fibrosing disorder, usually associated with a good prognosis, with spontaneous remission or remission after CS therapy. However, it is frequently associated with haematological disorders; to our knowledge, 25 cases of aplastic anaemia (AA) or pancytopenia in the setting of EF have been reported [1]. In these cases, although the semiological description of dermatological abnormalities was often poor, clinical signs of SSc were often absent. EF and SSc are generally considered to be two distinct diseases.